

Listing of Claims:

The Listing of Claims set forth below shall replace all prior versions and listings of claims in the application.

1. (Currently Amended) A method of modifying a biological molecule by formation of a C-O bond, comprising the steps of contacting a biological molecule which is a substrate for a polypeptide selected from the group consisting of:

(a) a polypeptide ~~comprised by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[[.]] 3;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence set forth in SEQ ID NO. 2; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under highly stringent conditions to SEQ ID NO:₂[[.]] 2 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide modifies the biological molecule by formation of a C-O bond.

2. (Currently Amended) A method according to claim 1 further comprising the step of contacting the biological molecule modified by the polypeptide recited in claim 1 with a second polypeptide selected from the group consisting of:

(a) a polypeptide ~~comprised by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[[.]] 5;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence set forth in SEQ ID NO:₂[[.]] 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO:₂[[.]] 4 and capable of C-O bond formation;

whereby said second polypeptide further modifies the biological molecule by formation of a C-O bond.

3. (Original) A method according to claim 1 wherein the C-O bond formed is between the biological molecule and a second biological molecule, said second biological molecule also a substrate for the polypeptide.

4. (Original) A method according to claim 1 wherein said contacting is in a host cell.

5. (Original) A method according to claim 4 wherein said host cell is a bacterium.

6. (Original) A method according to claim 4 where the host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

7. (Original) A method according to claim 4 wherein said biological molecule is an exogenously supplied substrate.

8. (Original) A method according to claim 1 wherein the contacting is *ex vivo*.

9. (Original) A method according to claim 1 wherein said method produces a macrotetralide or a macrotetralide analogue.

10. (Currently Amended) A method of catalyzing a C-O bond between biological molecules, comprising the steps of contacting biological molecules which are substrates for at least one polypeptide capable of catalyzing C-O bond formation between said biological molecules and encoded by a nucleic acid set forth in SEQ ID NO:₂[[.]] 1 or a nucleic acid hybridizing under stringent conditions thereto, with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

11. (Original) A method according to claim 10 wherein said contacting is in a host cell.

12. (Original) A method according to claim 11 wherein said host cell is a bacterium.

13. (Original) A method according to claim 11 wherein said host cell is a eukaryotic cell selected from the group consisting of a mammalian cell, a yeast cell, a plant cell, a fungal cell, and an insect cell.

14. (Original) A method according to claim 11 wherein at least one of said biological molecules is an exogenously supplied substrate.

15. (Original) A method according to claim 10 wherein the contacting is *ex vivo*.

16. (Original) A method according to claim 10 wherein said method produces a macrotetralide or a macrotetralide analogue.

17. (Currently Amended) A method of producing a macrotetralide or a macrotetralide analogue, comprising the steps of contacting biological molecules that are substrates for at least one polypeptide selected from the group consisting of:

(a) a polypeptide ~~encoded by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[.]] 3 or 5;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence set forth in SEQ ID NO:₂[.]] 2 or 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO:₂[.]] 2 or 4 and capable of C-O bond formation;

with said polypeptide under conditions such that the polypeptide catalyzes a C-O bond between the biological molecules and a macrotetralide or macrotetralide analogue is thereby synthesized; and

recovering said macrotetralide or macrotetralide analogue.

18. (Original) A method according to claim 17 wherein said method is carried out in a host cell and at least one biological molecule is an exogenously supplied substrate.

19. (Withdrawn) A method of preparing a hybrid enzyme comprising the step of positioning in a hybrid enzyme at least one catalytic domain capable of catalyzing C-O bond formation between biological molecules, said catalytic domain encoded by a polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2 or 4;

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 or 4 and capable of C-O bond formation.

20. (Withdrawn) A method of preparing a megasynthetase comprising the step of positioning in a megasynthetase at least one module including a polypeptide capable of catalyzing C-O bond formation between biological molecules, said polypeptide selected from the group consisting of:

(a) a polypeptide encoded by an amino acid sequence set forth in SEQ ID NO. 3 or 5;

(b) a polypeptide encoded by a nucleic acid comprising nucleotide sequence set forth in SEQ ID NO. 2 or 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO. 2 or 4 and capable of C-O bond formation.

21. (Currently Amended) A method of catalyzing C-O bond formation between biological molecules, comprising steps of contacting biological molecules that are substrates for a polypeptide selected from the group consisting of:

(a) a polypeptide ~~comprised by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[.] 3;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence set forth in SEQ ID NO:₂[.] 2; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under very stringent conditions to SEQ ID NO:₂[.] 2 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

22. (Original) A method according to claim 21 wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

23. (Currently Amended) A method of catalyzing C-O bond formation between biological molecules, comprising steps of contacting biological molecules that are substrates for a polypeptide selected from the group consisting of:

(a) a polypeptide ~~comprised by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[.] 5;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence set forth in SEQ ID NO:₂[.] 4; and

(c) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO:₂[.] 4 and capable of C-O bond formation;

with said polypeptide whereby said polypeptide catalyzes C-O bond formation between the biological molecules.

24. (Original) A method according to claim 23 wherein said method is performed in a host cell and at least one of the biological molecules is an exogenously supplied substrate.

25. (Currently Amended) A method of chemically modifying a biological molecule by formation of a C-O bond, comprising contacting a biological molecule that is a substrate for a polypeptide selected from the group consisting of:

(a) a polypeptide ~~encoded by~~ consisting of an amino acid sequence set forth in SEQ ID NO:₂[₁] 3 or 5;

(b) a polypeptide encoded by a nucleic acid ~~comprising~~ consisting of a nucleotide sequence identical to or isolated from SEQ ID NO:₄[₁] 1, 2 or 4;

(c) a polypeptide encoded by a nucleic acid encoding an amino acid sequence set forth in SEQ ID NO:₂[₁] 3 or 5; and

(d) a polypeptide encoded by a nucleic acid that specifically hybridizes under moderately stringent conditions to SEQ ID NO:₄[₁] 1, 2 or 4;

with said polypeptide whereby said polypeptide chemically modifies the biological molecule by formation of a C-O bond.